General

Guideline Title

Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases.

Bibliographic Source(s)

Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS, American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Jul;54(1):328-43. [95 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Tavill AS. Diagnosis and management of hemochromatosis. Hepatology 2001 May;33(5):1321-8. [50 references]

Recommendations

Major Recommendations

The grading system for the class of recommendations (1-2) and the levels of evidence (A–C) is defined at the end of the "Major Recommendations" field.

Clinical Features

1. The guideline developers recommend that patients with abnormal iron studies should be evaluated as patients with hemochromatosis, even in the absence of symptoms. (A)
2. All patients with evidence of liver disease should be evaluated for hemochromatosis. (1B)

Diagnosis

3. In a patient with suggestive symptoms, physical findings, or family history, a combination of transferrin saturation (TS) and ferritin should be obtained rather than relying on a single test. (1B) If either is abnormal (TS ≥45% or ferritin above the upper limit of normal), then *HFE* mutation analysis should be performed. (1B)
4. Diagnostic strategies using serum iron markers should target high-risk groups such as those with a family history of hereditary hemochromatosis (HH) or those with suspected organ involvement. (1B)

Family Screening

5. The guideline developers recommend screening (iron studies and *HFE* mutation analysis) of first-degree relatives of patients with *HFE*-related HH to detect early disease and prevent complications. (1A)

Liver Biopsy

6. Liver biopsy is recommended to stage the degree of liver disease in C282Y homozygotes or compound heterozygotes if liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) are elevated or if ferritin is >1000 µg/L. (1B)

Role of Liver Biopsy in Non–*HFE*-related HH

7. Liver biopsy is recommended for diagnosis and prognosis in patients with phenotypic markers of iron overload who are not C282Y homozygotes or compound heterozygotes. (2C)
8. The guideline developers recommend that in patients with non–*HFE*-related HH, data on hepatic iron concentration is useful, along with histopathologic iron staining, to determine the degree and cellular distribution of iron loading present. (2C)

Treatment of Hemochromatosis

9. Patients with hemochromatosis and iron overload should undergo therapeutic phlebotomy weekly (as tolerated). (1A) Target levels of phlebotomy should be a ferritin level of 50-100 µg/L. (1B)
10. In the absence of indicators suggestive of significant liver disease (ALT, AST elevation), C282Y homozygotes who have an elevated ferritin (but <1000 µg/L) should proceed to phlebotomy without a liver biopsy. (1B)
11. Patients with end-organ damage due to iron overload should undergo regular phlebotomy to the same endpoints as indicated above. (1A)
12. During treatment for HH, dietary adjustments are unnecessary. Vitamin C supplements and iron supplements should be avoided. (1C)
13. Patients with hemochromatosis and iron overload should be monitored for reaccumulation of iron and undergo maintenance phlebotomy. (1A) Target levels of phlebotomy should be a ferritin level of 50-100 µg/L. (1B)
14. The guideline developers recommend treatment by phlebotomy of patients with non-*HFE* iron overload who have an elevated hepatic iron concentration (HIC). (1B)

Treatment of Secondary Iron Overload

15. Iron chelation with either deferoxamine mesylate or deferasirox is recommended in iron overloaded patients with dyserythropoietic syndromes or chronic hemolytic anemia. (1A)

General Population Screening

16. Average risk population screening for HH is not recommended (Andersen et al., 2004). (1B)

Definitions:

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)	
Strength of Recommendation	Criteria
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, or higher cost or resource consumption
Quality of Evidence	Criteria
High (A)	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate (B)	Further research may change confidence in the estimate of the clinical effect
Low (C)	Further research is very likely to impact confidence on the estimate of clinical effect

Clinical Algorithm(s)

An algorithm for testing and treatment for hereditary hemochromatosis (HH) is provided in the original guideline document.

Scope

Disease/Condition(s)

- Hereditary hemochromatosis
- Secondary iron overload

Guideline Category

Diagnosis

Management

Screening

Treatment

Clinical Specialty

Gastroenterology

Medical Genetics

Intended Users

Physicians

Guideline Objective(s)

To suggest preferred approaches to the diagnostic, therapeutic, and preventative aspects of care for hemochromatosis

Target Population

- Individuals with suggestive symptoms, physical findings, or family history of hemochromatosis (*diagnosis*)
- First-degree relatives of patients with confirmed hereditary hemochromatosis (*screening*)
- Individuals with confirmed hereditary hemochromatosis or secondary iron overload (*treatment*)

Interventions and Practices Considered

Diagnosis/Screening

1. Transferrin saturation (TS)
2. Serum ferritin determination
3. *HFE* mutation analysis
4. Screening of first-degree relatives of patients diagnosed with *HFE*-related hereditary hemochromatosis (HH)
5. Liver biopsy, including hepatic iron concentration and histopathologic iron staining

Note: Screening of populations at average risk for HH was considered but not recommended.

Treatment/Management/Risk

Hereditary Hemochromatosis

1. Phlebotomy
2. Avoidance of vitamin C and iron supplements
3. Monitoring for reaccumulation of iron

Secondary Iron Overload

Iron chelation therapy with deferoxamine mesylate or deferasirox

Major Outcomes Considered

- Sensitivity and specificity of diagnostic screening tests for iron overload
- Iron levels
- Progression and complications of liver disease (e.g., cirrhosis, hepatocellular carcinoma)
- Morbidity and mortality

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline authors electronically searched PubMed using identifiers of hemochromatosis and haemochromatosis. There was no language restriction. Relevant papers were also identified from literature by consulting with personal databases collected by the authors. Searches were supplemented by reviewing the reference lists of all citations that met the final inclusion criteria, and by screening the first 50 citations in the "See related articles" function on PubMed of the included abstracts and articles. There was no specific time frame restriction in the search, but the goal was to provide new information since the previous American Association for the Study of Liver Diseases (AASLD) guideline on this topic, which was published in 2001. References in this document were from 1980 - 2010.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence*

Quality of Evidence	Criteria

Quality of Evidence	Criteria
High (A)	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate (B)	Further research may change confidence in the estimate of the clinical effect
Low (C)	Further research is very likely to impact confidence on the estimate of clinical effect

*Classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup with minor modifications.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These recommendations are based on the following: (1) a formal review and analysis of the recently published world literature on the topic; (2) the American College of Physicians *Manual for Assessing Health Practices and Designing Practice Guidelines*; (3) guideline policies including the American Association for the Study of Liver Diseases (AASLD) Policy on the *Development and Use of Practice Guidelines* and the American Gastroenterological Association's *Policy Statement on the Use of Medical Practice Guidelines*; and (4) the experience of the authors in regard to hemochromatosis.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations*

Strength of Recommendation	Criteria
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
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Cost Analysis

Economic models that have included genetic testing have suggested that population screening for hereditary hemochromatosis (HH) would be effective if only 20% of patients developed life-threatening complications. The natural history of untreated HH has been illustrated in the Copenhagen Heart Study, where patients were followed for 25 years with serial ferritin testing without an awareness that they were C282Y homozygotes. Many patients did not demonstrate progression of iron overload as measured by serum ferritin, and the costs of investigating false

positive iron tests in a screening program were considered significant. This has led some to consider that a genetic test should be done first, followed by measurement of serum ferritin. There have been concerns expressed about the adverse effects of genetic testing such as genetic discrimination; however, several studies have demonstrated that this is rarely a valid concern. Nonetheless, widespread population screening for HH is not recommended, whereas more selective screening in high-risk populations needs further study.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This practice guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases (AASLD). This committee provided extensive peer review of the manuscript, and Yngve Falck-Ytter, M.D., provided an external review from the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system perspective.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Andersen RV, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard BG. Hemochromatosis mutations in the general population: iron overload progression rate. Blood. 2004 Apr 15;103(8):2914-9. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of hereditary hemochromatosis (HH)

Potential Harms

- Recently, deferasirox (Exjade), an orally administered iron-chelating drug, has been approved in the United States for treatment of secondary iron overload due to ineffective erythropoiesis. Studies are ongoing regarding its potential use in hereditary hemochromatosis (HH). However, recent concerns about complications have tempered enthusiasm for this drug in HH.
- The application of deferoxamine therapy is limited by cost, the need for a parenteral route of therapy, discomfort, inconvenience, and neurotoxicity. Monitoring iron reduction in patients with secondary iron overload is challenging.
- The risks of liver biopsy have been reviewed, with mild bleeding after biopsy reported to be in the range of 1%-6%, and mortality associated with a complication of less than 1:10,000.

Qualifying Statements

Qualifying Statements

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible in contrast to standards of care, which are inflexible policies to be followed in every case.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2001 May (revised 2011 Jul)

Guideline Developer(s)

American Association for the Study of Liver Diseases - Nonprofit Research Organization

Source(s) of Funding

American Association for the Study of Liver Diseases (AASLD)

AASLD does not accept corporate support for the development of practice guidelines. However, AASLD gratefully acknowledges the support of Genentech and Merck for providing independent medical education grants for mobile download applications for AASLD practice guidelines.

Guideline Committee

Practice Guidelines Committee

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Financial Disclosures/Conflicts of Interest

Potential conflict of interest: Nothing to report.

Guideline Status

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site .

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org ; e-mail: aasld@aasld.org.

Availability of Companion Documents

This guideline is available for a variety of mobile devices via the APPRISOR™ Document Viewer from www.apprisor.com

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on May 9, 2003. The information was verified by the guideline developer as of June 12, 2003. This NGC summary was updated by ECRI Institute on January 6, 2012.

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